

Clinical Update

High-sensitive troponin T measurements: what do we gain and what are the challenges?

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Cardiac troponin (cTn) I and T are structural proteins unique to the heart. Detection of cTn in peripheral blood indicates cardiomyocyte damage. As acute myocardial infarction (AMI) is the most important cause of cardiomyocyte damage, cTns have become an integral part in the diagnosis of AMI. For this indication, cTns are superior to all other biomarkers and therefore are the preferred marker for the diagnosis of AMI. However, cTn indicates and provides an estimate of cardiomyocyte damage irrespective of its cause. The major limitation of contemporary cTn assays is that they are often not elevated during the initial hours of AMI. Recent advances in assay technology have led to more sensitive and precise cTn assays that will have a profound impact on clinical practice. High-sensitive cTn (hs-cTn) assays have two differentiating features from contemporary cTn assays: (i) detection of cTn in a majority of healthy persons and (ii) precise definition of what is 'normal' (=the 99th percentile). Recent multicentre studies have shown that hs-cTn assays improve the early diagnosis of patients with suspected AMI, particularly the early rule-out. To achieve best clinical use, cTn has to be interpreted as a quantitative variable. Rising and/or falling levels differentiate acute from chronic cardiomyocyte damage. The terms 'troponin-positive' and 'troponin negative' should therefore be avoided. 'Detectable' levels will become the norm and will have to be differentiated from 'elevated' levels. The differential diagnosis of a small amount of cardiomyocyte damage and therefore minor elevations of cTn is broad and includes acute and chronic cardiac disorders. The differential diagnosis of larger amount of injury and therefore more substantial elevations of cTn is largely restricted to AMI, myocarditis, and a rare patient with tako-tsubo cardiomyopathy.

Keywords

High-sensitive cardiac troponin • Diagnosis • Acute myocardial infarction • Sensitivity • Specificity

Introduction

Recent advances in assay technology have led to a refinement in cardiac troponin (cTn) I and T assays and therefore the clinical ability to detect and quantify cardiomyocyte injury.^{1–3}

Cardiac troponins are structural proteins unique to the heart. Detection of cTn in peripheral blood indicates cardiomyocyte damage. It is an unresolved issue whether cardiomyocyte damage as indicated by cTn always reflects myocardial cell death.^{1,4–6} In the absence of a sufficiently sensitive *in vivo* method to prove the integrity of the cardiomyocytes despite cTn release, we suggest that any damage identified by cTn release should be considered irreversible. This concept is supported by autopsy studies indicating substantial loss of cardiomyocytes during the course of life.⁷

As acute myocardial infarction (AMI) is the most important cause of myocardial cell death, the use of high-sensitive cTns

(hs-cTns) might be expected to lead to important improvements in the diagnosis AMI.⁸ This review will highlight the most relevant aspects of the issues involved from a clinical perspective and provide suggestions on how to best clinically apply hs-cTns.

Is there an unmet clinical need that high sensitivity cTns could assist with? We would suggest that there are at least two.

Early and reliable diagnosis of acute myocardial infarction

Acute myocardial infarction is the major cause of death and disability worldwide with an ongoing increase in incidence. The risk of death is highest within the first hours from AMI onset.^{9–11} Approximately 15–20 million patients per year present to the emergency department (ED) with acute chest pain or other symptoms

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suggestive of AMI in Europe and the USA.^{9–11} Rapid identification of patients at risk facilitates effective evidence-based medical treatment and management.^{10–12} In addition, since the majority of patients presenting with acute chest pain do NOT have acute ischaemia, but rather benign disorders, the rapid identification of these patients would substantially reduce ED overcrowding, which is a major problem associated with increased morbidity and even mortality in multiple studies.¹³

The 12-lead electrocardiogram (ECG) and cTn are the diagnostic cornerstones and complement clinical assessment (Figures 1 and 2).^{10–12} In most patients with ST-elevation AMI, clinical assessment and the ECG provide a straightforward diagnosis and allow the initiation of revascularization within minutes. However, ST-elevation AMI represents only about 5% of consecutive patients presenting with acute chest pain.¹⁴ Therefore, in many other patients, in fact the vast majority, the physician is left with considerable uncertainty after the clinical assessment and the initial ECG. The ECG by itself is often insufficient to diagnose as AMI ST deviation is non-specific and is observed in other conditions such as early repolarization patterns, acute pericarditis, left ventricular hypertrophy, left bundle branch block, hyperkalaemia, and the Brugada syndrome.^{10–12,15,16} Therefore, cTn values have a prominent role in the diagnosis of AMI and in identifying patients with acute coronary syndromes at high risk who will benefit from aggressive anticoagulation with antithrombin agents, IIB/IIIA platelet agents,^{10–12,17–22} early coronary angiography, and whenever possible percutaneous coronary intervention.^{14,16} Cardiac troponins which are sensitive and specific biochemical markers of cardiomyocyte damage are helpful in clinical practice in identifying patients with acute coronary syndromes at high risk and in selecting those patients who will benefit from early non-invasive and invasive treatment such as coronary angiography and whenever possible percutaneous coronary intervention.^{17–22} In addition, fully automated standard cTn assays are superior to other biomarkers that have been clinically available for the diagnosis of AMI and therefore are considered the preferred marker in the diagnosis of AMI.^{18,20,23–25}

A major limitation of the earlier generations of cTn assays is that they have a period during the first hours of AMI where they are not elevated. With these assays, circulating levels become detectable in peripheral blood only after 3–4 h.^{10–12,26} Thus, the diagnosis of AMI can require prolonged monitoring over 6–12 h and serial blood sampling (Figure 2) because there often is substantial ambiguity about the time of onset of any given ischaemic event. Delays in ‘ruling in’ AMI delay therapy and may increase morbidity and potentially mortality in AMI.^{10–12} Delays in ‘ruling out’ contribute to overcrowding in the ED and the associated costs probably exceeding several billion US dollars each year.²⁷

Figure 3 highlights the main difference between contemporary and hs-cTns assays. High-sensitive cTn assays have two differentiating features from contemporary cTn assays: (i) detection of cTn in a larger number of healthy persons and (ii) a more precise definition of what is ‘normal’ (=the 99th percentile).^{12,14,28} This feature is of key importance as a cTn value above the 99th percentile of a normal reference population is a ‘condition sine qua non’ for the diagnosis of AMI.

Detection of other disease entities that damage the heart and adversely influence prognosis

A variety of processes can lead to increases in cTn and they invariably reflect a significant structural or functional cardiac abnormality, usually with important prognostic significance. For example, elevations identify patients with adriamycin cardiotoxicity^{29,30} and those with severe carbon monoxide toxicity³¹ and help to identify high-risk patients who are acutely ill.³² More sensitive and more precise diagnosis will likely help to identify more such disease entities and thus provide opportunities to improve patient care and with it prognosis. The landmark work of Cardinale et al. in diagnosing and development effective treatments for adriamycin cardiotoxicity serve as a prescient example.²⁹

High-sensitive cardiac troponin assays

‘Sensitive’ and ‘high-sensitive’ are used by the manufacturer to describe their assays with increased sensitivity.^{33–35} Although there is no consensus when the terms ‘sensitive’ and ‘high or ultra-sensitive’ should be applied in the description of cTn assays, it is important to note that there are substantial analytical differences among the new assays. Some allow the detection of cTn in ~50% of a normal reference population and other in up to 90% of a normal reference population (Figure 3). One reasonable option is to use ‘sensitive’ for the former and ‘high-sensitive’ for the later.^{36,37}

Gain: sensitive and high-sensitive cardiac troponin assays improve the early diagnosis of acute myocardial infarction

Two large prospective multicentre studies have demonstrated that sensitive cTn and hs-cTn assays have a higher diagnostic accuracy at the time of presentation for the diagnosis of AMI than less sensitive cTn assays (Figure 4). The benefit observed for sensitive and high-sensitive assays was most pronounced in patients presenting early after chest pain onset.^{37,38} Many of the assays used in these studies are available for routine use but often have been used with cut-off values higher than the 99th percentile value. Regardless of the assay, the use of the 99th percentile value is essential for the optimal use of any cTn assay. Improvements in the early diagnosis of AMI in the ‘early presenters’ would offer the opportunity to test again whether early intervention in non-ST-elevation myocardial infarction (STEMI) patients might be beneficial as it is in STEMI patients.^{10–12} It may be that late presentation combined with the substantial time it takes to confirm the diagnosis has contributed substantially to the negative trials in this area. In addition, the sensitive cTn and hs-cTn assays will allow the reliable ‘rule out’ of AMI within a much shorter period than standard cTn assays. Used in

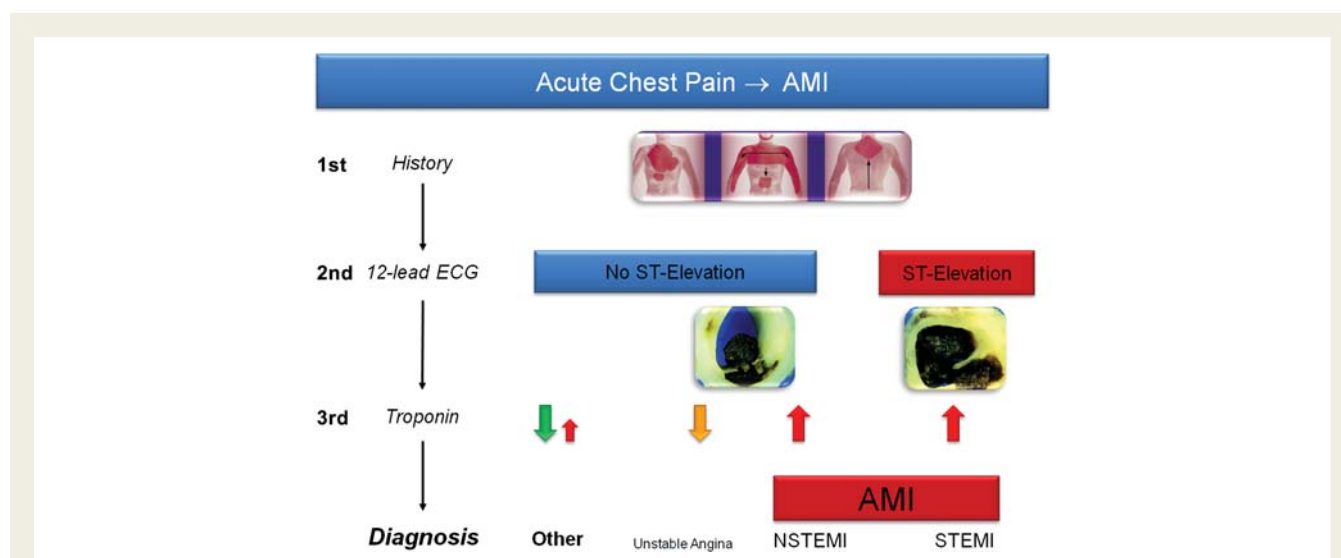


Figure 1 Twelve-lead electrocardiogram and measurement of cardiac troponin complement clinical assessment in the diagnosis of acute myocardial infarction. The unstable angina group is very likely to shrink significantly with the use of sensitive and high sensitivity cardiac troponin assays.

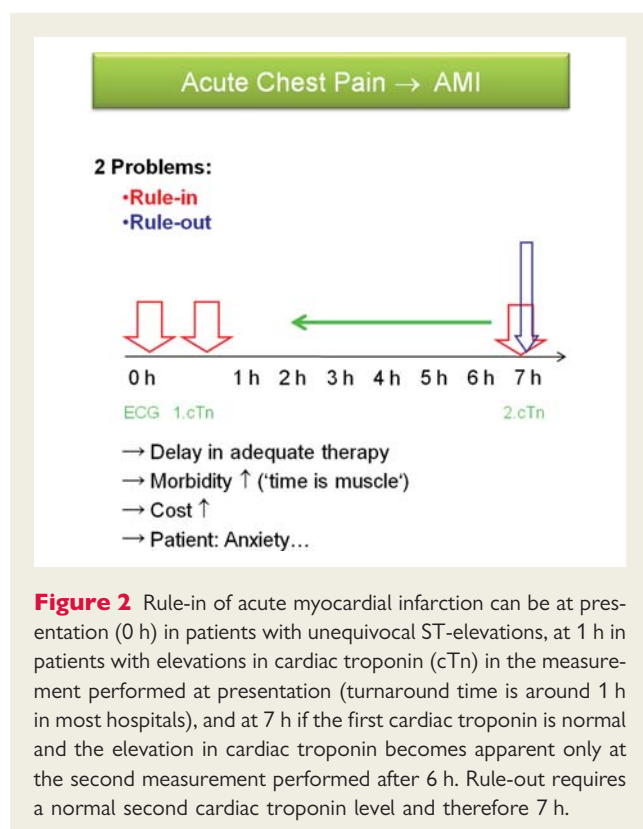


Figure 2 Rule-in of acute myocardial infarction can be at presentation (0 h) in patients with unequivocal ST-elevations, at 1 h in patients with elevations in cardiac troponin (cTn) in the measurement performed at presentation (turnaround time is around 1 h in most hospitals), and at 7 h if the first cardiac troponin is normal and the elevation in cardiac troponin becomes apparent only at the second measurement performed after 6 h. Rule-out requires a normal second cardiac troponin level and therefore 7 h.

conjunction with clinical assessment and the ECG, sensitive cTn and hs-cTn assays may significantly reduce the percentage of patients with diagnostic uncertainty who require continuous ECG monitoring and serial blood sampling. They also have the potential to obviate the need for subsequent stress testing. The

cost-savings associated with this increase in earlier and more comprehensive diagnostic accuracy might be substantial.²⁷ Ongoing studies by our group and others will define the best algorithms on how to apply these cTn assays to most rapidly rule-out and rule-in AMI. It is very likely that the novel high-sensitivity assays mentioned above will facilitate this process. For now, it appears that although reduced, there still may be patients with unstable angina without elevations in cTn that may require urgent care but this issue will require additional data. One may eventually (sic) be able to argue that without an increase in cTn, an unstable syndrome is not present.

The universal definition of AMI in 2007 identified different subtypes of AMI for the first time.¹² The designation of AMI is no longer restricted to those with acute coronary plaque rupture resulting in decreased oxygen supply (Type I) but also in conditions with elevated oxygen demand (Type II, e.g. sepsis, hypertensive crisis, tachycardic atrial fibrillation) in the absence of a dominant coronary atherosclerosis, endothelial dysfunction, vasospasm, or coronary embolism.^{39,40} It is opined that values of cTn may be lower in this group. If so, with the clinical launch of hs-cTn assays, this type of AMI will be diagnosed more often and it still has to be shown whether these patients profit from acute implementation of aggressive dual platelet inhibition, aggressive anti-coagulation, and an early invasive strategy as those with acute plaque rupture seem to.

Challenge: how to identify the cause of cardiomyocyte damage?

The hs-cTnT assay is the first hs-cTn assay available for widespread clinical application. Following the publication of the data showing superior performance in the early diagnosis of AMI, also various clinically important subgroups such as the elderly,⁴¹ many

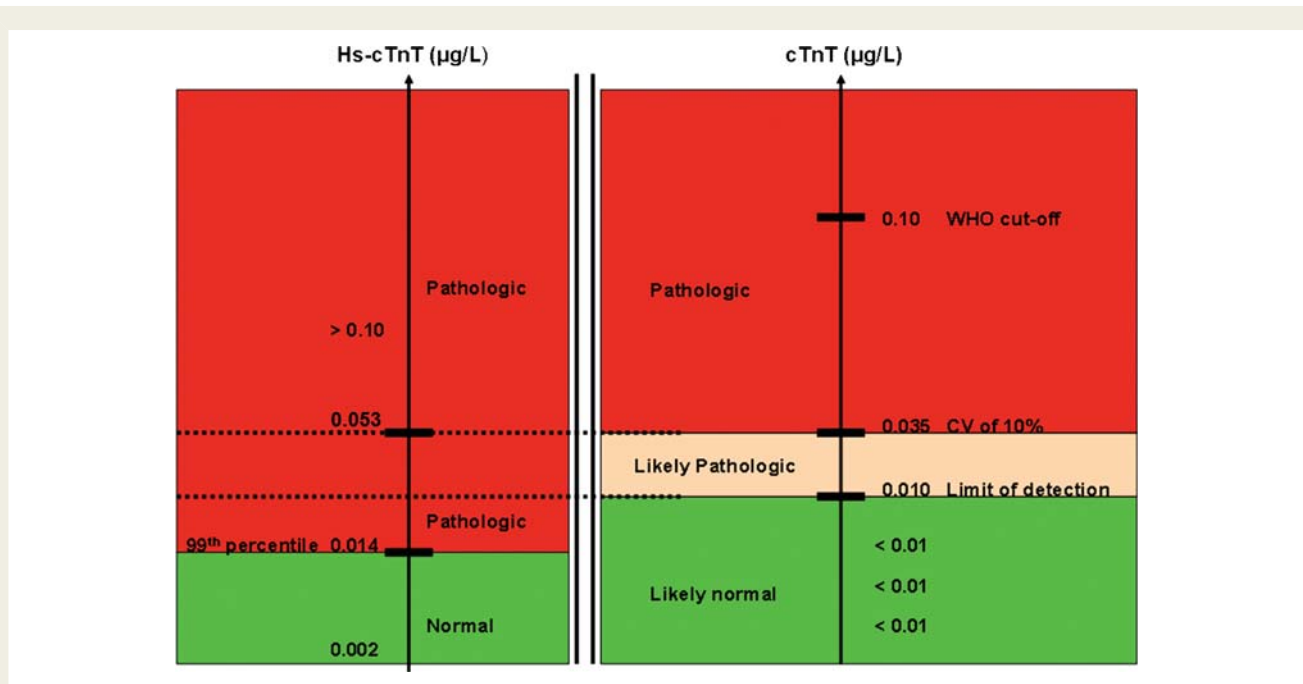


Figure 3 Interpretation of cardiac troponin concentrations in clinical practice, and changes offered by the consideration high-sensitive cardiac troponin. The main difference between contemporary cardiac troponin T (right, fourth-generation Roche cTnT) and high-sensitive cardiac troponin T (left) is that the latter allows a precise definition of the normal range. For cardiac troponin T, two different cut-off levels have been used. Levels of $<0.01 \mu\text{g/L}$ are undetectable and considered 'normal'. Levels between 0.01 and $0.035 \mu\text{g/L}$ are 'likely pathological' but associated with high imprecision, and levels above $0.035 \mu\text{g/L}$ are pathological. The high-sensitive cardiac troponin T assay detects many patients with previously undetectable cardiac troponin T levels who have high-sensitive cardiac troponin T levels above the 99th percentile explaining why most of these patients appear to be at risk.

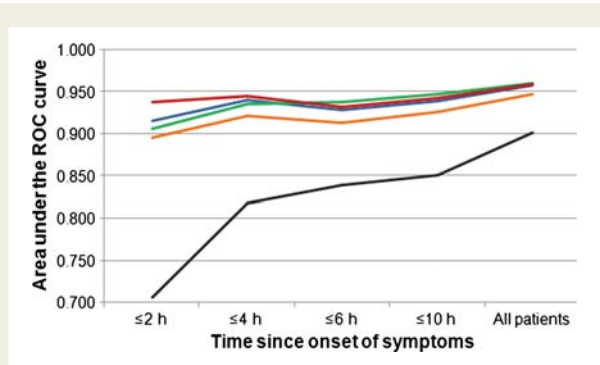


Figure 4 Diagnostic accuracy at presentation as quantified by the area under the receiver operating characteristic (ROC) curves for a contemporary cardiac troponin assay (black, fourth-generation cardiac troponin T) and four sensitive or high-sensitive cardiac troponin assays (red, Siemens cTnI Ultra; blue, Abbott cTnI Architect; green, Roche high-sensitivity cTnT; orange, Roche cTnI) in the diagnosis of acute myocardial infarction according to chest pain onset.

institutions throughout Europe have replaced the contemporary cTnT assay with the hs-cTnT assay. While this transition is technically easy as both assays run on the same platform and the hs-cTnT assay is comparably priced, the challenges faced on the clinical side

have been substantial and largely underestimated. Many institutions have switched assays with little educational efforts to prepare their clinicians on how to best apply the hs-cTnT test results.

Also, many institutions in Europe and in the USA are ill-prepared for the transition to the hs-cTn assays. Although some already were using a sensitive cTn assay, many institutions did not apply the cut-off level suggested by the current guidelines (the 99th percentile or even, though not recommended, the first higher concentration, fulfilling a coefficient of variation of less than 10%),^{12,14,28} but rather used a higher cut-off level because it provides higher specificity for AMI. This approach was recently studied with a contemporary assay and the use of a higher cut-off value was associated with substantial increases in morbidity and mortality than the use of a lower cut-off value in this study.⁴² However, it is important to note that the lower cut-off value applied was still higher than the 99th percentile, which would have been the cut-off value recommended in the universal definition.^{12,14,28}

For years, the clinical application of cTn results was rather simple. An elevated cTn level was considered equivalent to the diagnosis of an acute coronary syndrome and justified the immediate initiation of antiplatelet and anticoagulation therapy, transfer to the coronary care unit, and cardiology consultation for early coronary angiography and intervention.^{10–12,17–22}

The clinical introduction of sensitive and hs-cTn assays is a trade-off. They will allow the detection and eventually the exclusion of AMI in the first hours but also the detection of myocardial

cell death associated with multiple other pathophysiological situations as well and will challenge the clinician to differentiate them.

We are just beginning to understand the potential associated with the use of hs-cTn assays for these multiple other indications. These tools allow us to detect cardiomyocyte damage in the stable phase of established cardiac disease like coronary artery disease (CAD)⁴³ or heart failure, or even to identify in the general population those patients with either silent or clinically underestimated cardiac disease and therefore high risk of death.^{1–3,44} They facilitate the detection of the toxic effects of drugs and internal and/or external toxins which will in the long run lead to the avoidance of toxic treatments and approaches to mitigate the effects of those that cannot be avoided. Perhaps, had they been used during the development of peroxisome proliferator-activated receptor agonists and coxibs,⁴⁵ we might have avoided the difficulty associated with those therapies.

High-sensitive cardiac troponin improves risk stratification

It is instructive to use stable CAD as an example to discuss the potential clinical use and challenges associated with hs-cTn assays in risk stratification. In most patients with putatively stable CAD, cTn levels in peripheral blood are below the limit of detection for conventional assays. However, some of these patients do have elevations and they are associated with an adverse prognosis over time.^{46,47} In addition, detectable levels are more common in patients with disease undergoing angiography.⁴⁸ Recent data with the hs-cTnT assay from patients with stable CAD and preserved left ventricular ejection fraction function suggest that with high-sensitivity assays, more patients at risk can be identified.⁴³ High-sensitive cTnT levels were detectable in more than 90% of the patients and above the 99th percentile in 11% of the patients. After adjustment for several independent prognostic indicators, there was a strong and graded increase in the cumulative incidence of cardiovascular death and heart failure. In a large multiethnic population-based cohort, detectable levels of hs-cTnT were shown to be associated with higher all-cause mortality.³ Increased risk associated with higher levels of cTnT was evident well below the limit of detection of conventional cTn T assays and even below the 99th percentile of values in a healthy population. These data correlate nicely with the graded relationship between the extent of CAD and hs-cTnT shown by Laufer *et al.*⁴⁹ Of interest, men had higher values than women for any given anatomic subset. In a first attempt at defining subgroups in this area, Schulz *et al.*,⁵⁰ using a novel hs-cTnI assay, could not find a relationship to the extent of CAD or prognosis and high-sensitivity values in a cohort of putatively stable patients undergoing elective coronary angiography.

Given these data and the reference range data which suggest lower values in women,⁵¹ it may be that different values will be necessary based on gender. This could also be the case with race given the recent data of de Lemos *et al.*³ The next step now is to prove that we have treatment modifications to offer to patients identified to be at increased risk that ultimately improve patient outcome. Using a pre-commercial hs-cTnI assay in a heterogeneous group of patients with diverse aetiologies for cardiac

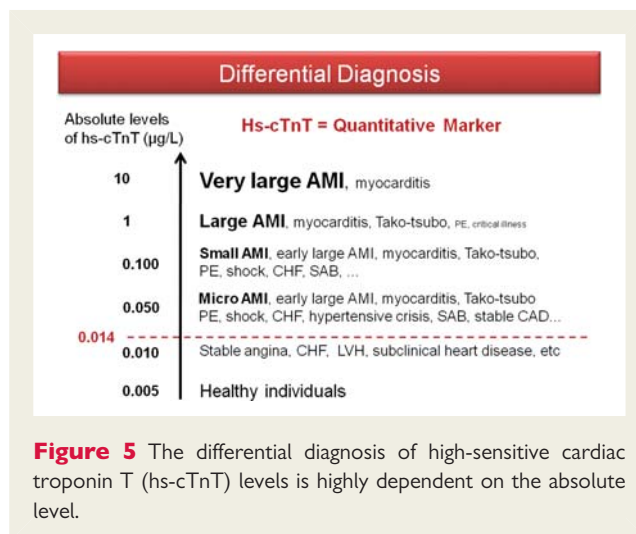


Figure 5 The differential diagnosis of high-sensitive cardiac troponin T (hs-cTnT) levels is highly dependent on the absolute level.

disease, values were not helpful in distinguishing the aetiology of the elevations or in predicting prognosis.⁵⁰

Clinical application of high-sensitive cardiac troponin assays: absolute level and change

Since AMI is not the only cause of cardiomyocyte damage, it is key to consider the absolute level as well as the change in cTn early after presentation as important criteria in the differential diagnosis of the cause of cardiomyocyte damage (Figure 5). Higher values are more often due to AMI and/or myocarditis. Thus, the higher the value of cTn at ED presentation, the higher the probability of AMI.^{1–3} The differential diagnosis of mild elevation of cTn and therefore mild cardiomyocyte damage is broad and includes both acute and chronic disorders. Thus, the terms troponin 'positive' and 'negative' should be avoided.

Secondly, the larger the rise in the hs-cTn within the first hours in the ED is, the higher is the probability that it is caused by AMI. When AMI is overt, marked changes are present with changes well over 100%.⁵² Chronic cardiac disease including stable angina exhibits more constant cTn levels. How to define a changing pattern of cTn is unsettled. Unresolved questions include whether to use absolute or relative changes to best separate acute from chronic cTn elevations, as well as the specific values for use in the diagnosis of AMI (what changes in what time interval). Several groups have advocated the use of a criterion of 50% based on the biological variation of another hs-cTn assay.⁵³ However, in a recent study, the area under the receiver operating characteristic (ROC) curve for diagnosing AMI was significantly higher for 2 h absolute vs. 2 h relative cTn changes. The ROC curve-derived cut-off value for 2 h absolute change was 0.007 µg/L for hs-cTnT and 0.020 µg/L for cTnI ultra (both cut-off levels are half of the 99th percentile of the respective cTn assay). Absolute changes were superior to relative changes in patients with both low and elevated baseline cTn levels.⁵⁴ Data from other groups will soon become available and help to provide more definite recommendations.

However, an ROC determined value is a balance between sensitivity and specificity and one might want, in this situation, to use the minimum delta associated with an acute event rather than the ROC value in the interest of not missing patients potentially at risk.

However, it is important to highlight that detailed clinical assessment remains mandatory to differentiate AMI from the other potential causes of myocardial injury. Some have advocated the use of biological variation to inform this measurement.^{55,56} At present, however, it is unclear what the proper metric is. Indeed, it is not the optimal delta that is of importance but the minimum delta that should inform this decision. It should also be appreciated that these highly sensitive assays and change criteria will be badly confounded by analytic problems such as haemolysis⁵⁷ and/or other analytic problems because such small changes are of importance.⁵⁸ Once we understand how to use these metrics, we will be able to address whether AMI and unstable angina are different or similar diseases on the myocardial level.⁵⁹

As indicated above, an elevated value of cTn is associated with drug toxicities, patients with acute heart failure, and critically ill patients as well. These elevations are highly prognostic.^{29,30,32} With hs-cTn assays, more such elevations will be detected.⁶⁰ The most appropriate management of these groups is still unknown but they are at greater short- and long-term risk and we have an obligation as clinicians to make sure that at least indicated prevented care of risk factors is undertaken.

Ongoing studies will define the best algorithms on how to apply the data from hs-cTn assays in clinical practice. Rule-out and rule-in algorithms as well as the timing of the second measurement will have to be fine-tuned for each specific cTn assay. Preliminary data suggest that the hs-cTn assays will allow the reliable rule-out of AMI in many patients within 1–3 h from presentation to the ED.^{11,12,61} It is important to note that the diagnostic performance of sensitive cTn assays in the diagnosis of AMI outside the setting of chest pain patients presenting to the ED is unknown.

The more widespread application of sensitive and hs-cTn tests and the application of the 99th percentile as the decision limit for AMI will lead to a substantial increase in the detection of patients with slightly elevated levels of cTn. In some of them, AMI will be the diagnosis, and in many others, the mechanisms of myocardial injury will not be AMI. Future studies need to define the most appropriate therapeutic measures in response to the detection of myocardial injury in many of these settings.

Sensitive and hs-cTn assays provide a new non-invasive window to the heart. We should not be afraid of having a closer look. Accepting that we do not fully understand all what we see through this novel window is a crucial step to direct future research in the right direction in order to improve the management of patients with cardiovascular disorders.

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CARDIOVASCULAR FLASHLIGHT

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Early calcific degeneration of a CoreValve transcatheter aortic bioprosthesis

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A 74-year-old man, one of the first few patients in the world to undergo transcatheter aortic valve implantation (TAVI) with the porcine CoreValve bioprosthesis presented with dyspnoea after 5 years. Echocardiogram and cardiac catheterization, respectively, revealed and confirmed bioprosthetic degenerative restenosis. The mean gradient across the CoreValve on transthoracic Doppler was 53 mmHg and pull-back gradient at catheterization was 79 mmHg. Aortic insufficiency was only mild. Of note, echocardiography 1 year earlier was unremarkable. In the absence of very high surgical risk, he underwent surgical bioprosthetic replacement. Extensive calcification of the explanted CoreValve's leaflets was noted both on the outflow and inflow surfaces. Although a rare event so early after CoreValve implantation, he was among the earliest patients. Appropriate patient selection and vigilance to determine long-term CoreValve durability is paramount, particularly with the interest in extending TAVI to lower-risk patients.

Figure: Degenerated CoreValve. Panel (A) shows the continuous wave Doppler tracing across the aortic bioprosthesis on transthoracic echocardiography with a mean gradient of 53 mmHg. Panel (B) demonstrates the aortic pull-back gradient of 79 mmHg during cardiac catheterization. Surgical extraction of the degenerated CoreValve prosthesis was performed (C). Panels (D) and (E) demonstrate the extensive calcification on the outflow and inflow aspects of the porcine leaflets, respectively.

